

Optimization of Multimodal and Multitemporal Deformable Image Registration for Head and Neck Cancer

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Abstract. With the growing interest in translating multimodal and functional imaging into the patient pathway it becomes important to accurately co-register the information from different imaging modalities at different timepoints. In this work we optimize and evaluate an open-source deformable image registration algorithm (NiftyReg) for CT and MR registrations in the head and neck region. The accuracy of the registrations was assessed using similarity between manual and deformed landmarks and structures. The properties of the deformation fields were also quantified.

1 Motivation

Over the last years there has been a growing interest in further introducing multimodal and functional magnetic resonance (MR) imaging into the patient treatment workflow. The additional and complementary information can potentially be used to improve the outcome of cancer radiotherapy treatments. To improve treatment planning multimodal and multiparametric imaging can be used to aid target delineation [1], for dose painting applications [2] and to decide on treatment strategies and beam arrangements considering the biological characteristics of the patient. In adaptive radiotherapy (ART) applications, it can be used as an early biomarker of the patient response and the additional anatomical and functional information can be fed into the treatment adaptation process. Early recognition of failure may allow alternative treatments to be explored, avoiding unnecessary radiation exposure and associated side effects [3]. Functional imaging also provides alternative methods to assess treatment outcome. Additionally, the treatment follow-up information may be correlated with the physical dose and biological properties of the tissue pre-therapy to develop predictive models of treatment outcome [4].

The ability to fully use clinically the biological information obtained with anatomical and functional imaging relies on the accuracy in co-registering the multiple sources of information. Therefore, accurate deformable image registration (DIR) is a key part in the different applications of multimodal and multiparametric imaging. In the head and neck (HN) region MR images are more challenging to register than other popular imaging modalities (such as CT or CBCT) for several reasons: (i) the image resolution is generally smaller and within certain volumes, such as the shoulders and thoracic area, the image quality is considerably poorer (ii) imaging patients in treatment positioning is not always possible due to coil placement and patient comfort, (iii) image-specific artifacts, such as those caused by the inhomogeneities of the magnetic field (bias), and field-of-view (FoV) clipping are common issues of current clinical acquisition protocols.

Validation of automatic DIR for multimodal and multitemporal data in the HN region in the context of radiotherapy is a rather unexplored topic in the literature. Leibfarth *et al.* use DIR between planning PET/MR and CT images for HN patients, comparing three different optimization metrics of a B-Spline DIR, for dose painting applications [5]. Slagmolen *et al.* present a small feasibility study on CT-MR and MR-MR DIR for radiotherapy treatment planning [6]. On a more technical side, some groups having been developing specialized DIR algorithms [7,8]. Other authors looked at various applications in different anatomical sites [9,10]. In this work the use of DIR for multimodal and multitemporal registrations in the HN region was investigated and optimized. An in-house DIR tool is used to co-register images from different modalities at similar time points (CT and MR) and from the same modality at different time points (MR), and the quality of the registrations was assessed using manually annotated structures. The properties of the deformation vector fields (DVF) were also assessed.

2 Methods and Materials

2.1 Patient data acquisition

A total of three head and neck datasets were used in this study. Each patient received a routine radiotherapy planning CT (pCT), a pre-treatment MR booked as close as possible in time to the pCT (MR₁), and a follow-up MR 6 months after treatment (MR₂). The MR study consisted of T₂-weighted sequences, but functional sequences were available for future studies. MR₁ was acquired in treatment position. The inclusion criteria of this study was solely based on minimizing acquisition issues characteristic of routine MR (such as clipping of the FoV), and not to select patients with smaller anatomical changes.

The imaging protocol consisted of a planning CT (GE Widebore 16 slice system, GE Healthcare, Little Chalfont, UK) with contrast injection and reconstructed with a resolution of 0.977×0.977×2.5 mm. The MR images were acquired using the MAGNETOM Avanto (Siemens Healthcare, Erlangen, Germany) MRI scanner (1.5T). In T₂-weighted images, TE varied between 90 and

110 ms, TR between 2400 and 8100 ms, slice thickness between 3 or 5 mm with a gap of 0.5 mm, and number of slices between 29 and 61. In addition, image resolution was $0.703 \times 0.703 \text{ mm}^2$ or $0.859 \times 0.859 \text{ mm}^2$.

2.2 Multimodal and multiparametric imaging in an ART workflow

For integration of MR data into the radiotherapy pathway, image registration is necessary between CT at the planning stage and repeat MR at different time points. To co-register multitemporal MRs with CT, two registration pathways can be followed:

1. the pos-RT MR is registered with the pre-RT MR, which is independently registered to the CT;
2. the pos-RT MR is registered directly with the CT.

In this work only the results from the first pathway were assessed quantitatively. Due to the 6 months gap between pCT and MR₂ we found that it was very challenging to tune the DIR parameters to be universally good, and in general the results were poor and physically implausible. Therefore, in our opinion it was a better approach to independently register similar anatomical information from different modalities at similar time points (pCT-MR₁) and anatomical deformations from the same modalities at different time points (MR₁-MR₂). This allows to decouple the difference in image intensity between modalities from the anatomical deformations that occur over time. Therefore, two registration methods were investigated:

- CT-MR₁: if the two images were acquired close in time and with same immobilization, a rigid registrations is the easier and natural approach. However, DIR can be used to compensate for residual setup errors. This may introduce additional issues, which will be investigated here.
- MR₁-MR₂: monomodal DIR was investigated to track over time changes in anatomy. The ability to map anatomy between timepoints also allows to propagate co-registered functional information (using the same DVFs as in the anatomical sequences).

2.3 Image registration settings

All the registrations were performed using the open-source DIR software NiftyReg (<http://cmic.cs.ucl.ac.uk/home/software/>). It includes a Block Matching based affine registration [11], and several B-spline Free Form Deformation based algorithms [12]. NiftyReg’s stationary velocity fields implementation was the algorithm chosen for the registrations [13]. This is a symmetric and inverse-consistent algorithm that explicitly generates the transformations in the forward and inverse direction.

A total of six registration parameters with variable weight of the bending-energy penalty terms (BE) and control point spacing (CPS) were investigated per registration type. The values of BE varied between 0.01% and 1%, while the CPS

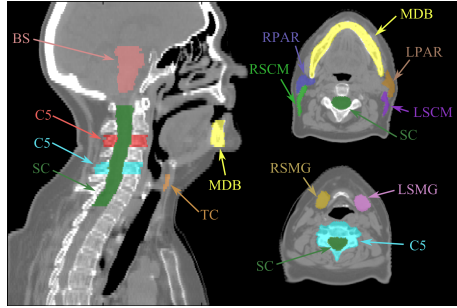


Fig. 1. Structure set manually delineated on the CT and MRs of each patient.

values tested ranged from 8 to 12 mm. NMI was chosen as similarity measure for multimodal registrations, and LNCC for monomodal registrations. LNCC was preferred over other monomodal similarity measures since it handles better the nonuniform biases that cause artifacts in MR images. To minimize the impact of artifacts due to field inhomogeneities, the MR images were corrected for bias using the N4ITK algorithm [14]. To avoid the optimization of the transformation in regions where there is no anatomical matching, the tumour was masked out in MR_1 - MR_2 registrations for patients where the gross tumour disappeared between MR_1 and MR_2 (as a result of the treatment). This avoids unrealistic deformations in these regions of no real one-to-one matching. The resulting deformation is a smooth interpolation between the mapping outside the mask, guided by the regularisation of the registration.

2.4 Quantitative analysis

The registrations were compared qualitatively, by visual inspection, and quantitatively by similarity of deformed points and structures with the manually delineated gold-standard. The registration quality was assessed in both directions.

A total of 12 structures were manually delineated on the CT, MR_1 and MR_2 by expert radiation oncologists. The structures chosen provided an indication of how well the registration accounted for anatomical differences and positioning errors (Fig. 1). It consisted of vertebrae C3 and C5, mandible, thyroid cartilage (bony anatomy), spinal canal, brainstem, parotids (organs at risk, OAR), submandibular gland and sternocleidomastoid muscles (soft tissues).

We calculated the dice similarity coefficient (DSC), which provides information about the similarity between volumes, and the distance transform (DT), which is the signed Euclidean distances between the manual and deformed surfaces and infers about the closeness between contours. We computed mean, standard deviation and 95% percentile of the DT distribution (DT_{mean} , DT_{std} and $DT_{95\%}$).

Additionally, the properties of the DVFs were assessed for all the registrations. The smoothness of the transformations was analysed using the harmonic

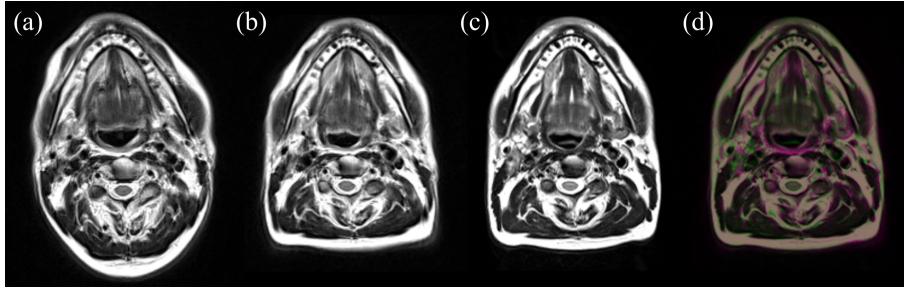


Fig. 2. Example of registrations: (a) MR_2 , (b) MR_1 , (c) MR_2 deformed to MR_1 , and (d) overlay between MR_1 (magenta) and deformed MR_2 (green).

energy (HE) and the properties of the determinant of the Jacobian of the transformation [$\det(\text{Jac})$]. The HE is inversely proportional to the smoothness of the deformation, while $\det(\text{Jac})$ indicates the level of expansion/contraction at each voxel with negative values indicating noninvertible and unrealistic deformations. Additionally, the inverse-consistency error (ICE) was calculated to investigate if the generated transforms were true inverses.

3 Results

Analysing the quantitative results obtained for all the registrations performed, we concluded that the combination of parameters that worked the best in our datasets were $BE=1\%$ and $CPS=12$ mm for $CT-MR_1$, and $BE=0.1\%$ and $CPS=12$ mm for MR_1-MR_2 . In $CT-MR_1$ registrations, we found it was preferable to use a higher weight of the BE than for MR_1-MR_2 . This reduced the risk of the registration causing additional uncertainties in comparison with rigid-only alignment (such as deformation of bones). However, if the immobilization is not present, those constraints should be relaxed to give the algorithm enough freedom to recover larger deformations. Since multimodal registrations had to capture larger anatomical changes the constraints had to be relaxed (Fig. 2), and the properties of the DVFs reflect also this. A higher CPS spacing in general resulted in DVFs with more desirable properties, which did not compromise the similarity between structures. For this combination of registration parameters, the mean and standard deviation obtained for the quantitative evaluation of the DIR can be found in Table 1.

Additionally to the global results provided in Table 1, we also looked at the results grouped by structure type. In MR_1-MR_2 registrations, the DSC values were 0.62 ± 0.12 , 0.77 ± 0.08 and 0.84 ± 0.07 for bony anatomy, soft tissues and OAR in DIR cases, and 0.4 ± 0.3 , 0.63 ± 0.18 and 0.65 ± 0.19 when using a rigid-only registration. The use of a rigid-only transform in MR_1-MR_2 registrations was not adequate, as we found that for some anatomical structures the overlap could be close to zero due to the large anatomical changes and differences in positioning between pre and post-RT scans. For $CT-MR_1$ registrations the DSC

Table 1. Qualitative assessment of the registrations (mean± standard deviation). The results are averaged for all patients, structures or DVFs, and registration directions.

		Similarity of structures		
	DSC	DT _{mean} (mm)	DT _{std} (mm)	DT _{95%} (mm)
CT-MR ₁	0.72±0.16	-0.1±1.8	2.2±1.2	6±4
MR ₁ -MR ₂	0.74±0.13	0.1±1.7	2.3±1.6	6±5
		Properties of the DVFs		
	HE	det(Jac) _{1%}	det(Jac) _{99%}	ICE _{mean} (mm)
CT-MR ₁	0.15±0.01	0.72±0.10	1.32±0.09	0.08±0.10
MR ₁ -MR ₂	0.39±0.06	0.5±0.3	1.7±0.3	0.8±0.7

values were 0.57 ± 0.18 , 0.79 ± 0.06 and 0.81 ± 0.04 for bony anatomy, soft tissues and OAR when using DIR, and 0.57 ± 0.18 , 0.74 ± 0.09 and 0.79 ± 0.04 when using rigid-only registrations. The results obtained with DIR and rigid-only registrations were very similar, with DIR performing marginally better in the soft tissue regions.

4 Discussion

Promising results were found for multimodal and multitemporal registrations. For the soft tissues and OARs, values found were in agreement with results from other multimodal studies [5,6], and comparable to monomodal or quasi-monomodal (CT-CT/CT-CBCT) studies [15,16]. In spite of the large deformations between pre and post-RT images, it was possible to achieve similar registration accuracy as for CT and MR in treatment position.

The registration of bony anatomy was poorer than for other types of structures. On one side, the reduced contrast between soft tissue and bone in MR difficulties the delineation of bones, particularly for complexly shaped structures such as the vertebrae, resulting in a non-ideal gold-standard. This low contrast also affects the quality of the registrations. However, the main interest in using MR is not to provide additional information on the bone anatomy (where CT is more relevant), but rather on the soft tissues. Thus misregistrations of the bones is of reduced importance when considering clinical applications and, in fact, in regions of higher clinical relevance, such as OAR and soft tissues, DIR performed in a higher level of accuracy. Nevertheless, the poor registration of the bones may affect nearby soft tissues so it is of importance to develop DIR strategies that account for the rigid behavior of bony anatomy.

We found that CT-MR₁ DIR slightly improved the anatomical matching in comparison to a rigid registration; however, the difference was not clinically significant. Additionally, we found that one must carefully tune its DIR registration to avoid introducing errors in this process. Further studies with a larger patient dataset are necessary to fully understand this additional uncertainty, and also to

validate CT-MR registrations for patients that can not acquire MR₁ in treatment position (i.e., with considerable setup variation between scans).

The FoV clipping was found to limit of the quality of the registrations. A clipped body contour reduces the ability to capture global deformations and generates unrealistic deformations within the patient near the edges of the FoV. For example, this was found to interfere in the registration of the mandible, which was very often clipped in the MR scans.

One of our main interests is to use multimodal and multiparametric MR imaging in the context of ART applications, which is becoming an increasingly relevant topic with the advent of the MR-Linac [17]. We acknowledge that our study is not ideal to validate the use of DIR for such applications, as the multiple MR were not acquired throughout the treatment. However we believe that using a pos-RT MR results in more challenging registrations, and therefore MR₂ can be considered a surrogate for MR acquired during treatment. This is however only true when considering the mapping of healthy tissues. Tracking of tumour volumes has to still be properly validated when the MRs are acquired throughout the course of radiotherapy. Additionally, the work here presented focused on anatomical information only, so future work will also focus on tracking functional information associated with the anatomical scans.

5 Conclusions

In this work we optimized an open-source DIR algorithm for the registration of CT and MR datasets of the head and neck. This is a first step toward incorporating additional imaging into the radiotherapy pathway.

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